

# A Clinician's Approach to the Diagnosis and Management of Recurrent Pregnancy Loss



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## KEYWORDS

- Recurrent pregnancy loss • Recurrent miscarriage
- Unexplained recurrent miscarriages • Diagnosis and management
- Controversial treatment

## KEY POINTS

- Recurrent pregnancy loss, a condition affecting 1% to 5% of couples, can be challenging for clinicians to manage and devastating to patients needing answers.
- Generally accepted guidelines on the diagnosis and treatment are reviewed.
- More than 50% of patients do not have a diagnosis for the cause of their miscarriages.
- Multiple treatment options have been used for unexplained recurrent miscarriage patients; however, evidence is lacking. Larger clinical trials are needed.

## INTRODUCTION

Miscarriage is a devastating event that can occur spontaneously in 15% of all clinically recognized pregnancies.<sup>1</sup> Up to 5% of women of reproductive age, however, experience recurrent pregnancy loss (RPL).<sup>2</sup> Statistics vary in the literature depending on which definition is used for RPL. Classically, RPL has been defined as the loss of 3 or more pregnancies before 20 weeks. Currently, researchers and the American Society for Reproductive Medicine (ASRM) have revised the definition of RPL to 2 or more failed consecutive pregnancies. Although many patients consider they are pregnant based on a home pregnancy test, ASRM defines clinical pregnancy as a pregnancy confirmed by ultrasonography or histopathologic examination.<sup>2</sup> Unfortunately, this definition leaves a lot of gray area, such as a well-documented biochemical pregnancy or a patient who experiences a home miscarriage without previous ultrasound and when the products of conception (POCs) are not examined. On the contrary, the Royal College of Obstetricians and Gynaecologists (RCOG) defines miscarriage as the loss of all pregnancies from the time of conception to 24 weeks, when the fetus would reach viability.<sup>3</sup> This broader definition of pregnancy and miscarriage is more practical

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The author declares that she has nothing to disclose.

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in the clinical setting when supporting grieving patients with a positive pregnancy test that did not result in a live birth.

The diagnosis and management of RPL can be both challenging and frustrating because there are both generally accepted and controversial etiologies and treatments. The controversy stems from the lack of large clinical trials, conflicting studies, or little to no evidence in the literature. Despite this deficit in evidence, well-intending clinicians continue to focus on theoretic etiologies and unproved treatments, which can lead to misleading results.<sup>4</sup> Unfortunately, 50% of RPL patients do not have a clear diagnosis despite a full work-up,<sup>5</sup> leaving clinicians and patients desperate for answers and treatment options. The goal of this article is, first, to review etiologies that have been associated with RPL and the recommended and controversial evaluation and management. Second, this article gives clinicians a proposed approach for the diagnosis and management of patients with this intimidating disorder.

## **RISK FACTORS AND MANAGEMENT OF RECURRENT PREGNANCY LOSS**

### ***Anatomic Etiologies***

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Uterine anomalies, both congenital and acquired, can account for up to 19% of RPLs.<sup>6</sup> Most commonly, congenital anomalies lead to second-trimester pregnancy loss. It is a debate on the role uterine malformations play in first-trimester RPLs but the assessment of the uterine cavity is generally recommended. Congenital uterine anomalies that potentially cause RPL include unicornuate, didelphic, bicornuate, septate, and arcuate uteri.<sup>2</sup> Due to the vascular insufficiency, septate uterus is the most common of the anomalies, causing up to 35% of RPLs.<sup>7</sup> Acquired anomalies that may contribute to RPL include fibroids, endometrial polyps, and uterine adhesions. The management of these issues, however, in regard to RPL is controversial. Uterine fibroids are the most common of the defects that are acquired, but their role in RPL and management is debatable and may depend on size and location to determine if surgical management is warranted. A majority of uterine anomalies can be detected in the office using saline infused 3-D ultrasound, which is also the most cost-effective test for evaluating the uterus. Other diagnostic studies performed outside of the office can include hysterosalpingogram, hysteroscopy, laparoscopy, and MRI.

It is the general consensus that surgical correction in patients with RPL who have significant uterine cavity defects should be considered. Particularly, in cases of women with RPL and septate defects, surgical correction may have some benefit although large randomized controlled studies are lacking.<sup>2</sup> The role of fibroids and RPL is not completely understood, but it has been stated that submucosal fibroids should be surgically removed when diagnosed in these women to increase pregnancy potential.<sup>8</sup>

### ***Genetic Etiologies***

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After 2 or 3 miscarriages, a genetic evaluation of the POCs and the parents should be considered early in the work-up. In couples with RPL, 3% to 5% have chromosomal abnormalities in 1 of the partners. Of these patients, the most common chromosomal anomaly associated with RPL is a balanced translocation,<sup>9</sup> a chromosomal anomaly in which there is an exchange of genetic material between chromosomes. Even though this is a small portion of RPL patients, this information can be the key in determining appropriate next steps and to give patients realistic expectations.

The most common cause of pregnancy loss at less than 10 weeks is embryonic aneuploidy. Cytogenic abnormalities account for at least 50% of all miscarriages. In couples with RPL, chromosomal anomalies occurred in the POCs 30% to 57% of

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